

MAR 24 2005

REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188	
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1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE 23.Mar.05	3. REPORT TYPE AND DATES COVERED MAJOR REPORT	
4. TITLE AND SUBTITLE RING-CLOSING METATHESIS OF MACROCYCLIC COMPOUNDS AND CROSS-METATHESIS OF ALLYL ESTERS OF AMINO ACIDS LEADING TO PEPTIDOMIMETICS			5. FUNDING NUMBERS	
6. AUTHOR(S) CAPT LOW TAMMY K				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) UNIVERSITY OF FLORIDA			8. PERFORMING ORGANIZATION REPORT NUMBER CI04-1008	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) THE DEPARTMENT OF THE AIR FORCE AFIT/CIA, BLDG 125 2950 P STREET WPAFB OH 45433			10. SPONSORING/MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION AVAILABILITY STATEMENT Unlimited distribution In Accordance With AFI 35-205/AFIT Sup 1			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 words)				
14. SUBJECT TERMS			15. NUMBER OF PAGES 3	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT	


TOPIC: Combinatorial, Parallel, and Solid Phase Chemistry

TITLE: Ring-Closing Metathesis of Macrocyclic Compounds and Cross-Metathesis of Allyl Esters of Amino Acids Leading to Peptidomimetics

AUTHORS: Tammy K.C. Low and Eric Enholm

The preparation of a dynamic combinatorial library of peptides using the cross-metathesis of allyl esters of amino acids was examined in a model study. This preliminary investigation employed Grubbs' second generation catalyst for the ring-closing metathesis of unique macrocyclic systems. An N-allyl lactam function, that was part of the large ring, was reacted with allyl esters of amino acids in a cross-metathesis coupling. The reversibility of the reaction, the modified amino acids, and the dynamic biomimetic aspects were all of interest in this study on new types of cyclic peptidomimetics.

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Ring-Closing Metathesis of Macrocyclic Compounds and Cross-Metathesis of Allyl Ester of Amino Acids Leading to Peptidomimetics

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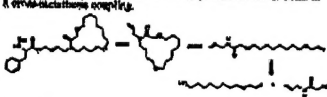
INTRODUCTION

Ring-closing and cross-metathesis reactions are important tools in organic synthesis. The reversibility of cross-metathesis makes it ideal for use in dynamic combinatorial chemistry. In particular, we are interested in generating a library of new cyclic peptidomimetics. The reversibility of the reaction, the required amino acids, and the dynamic combinatorial aspects are all of interest in this study.

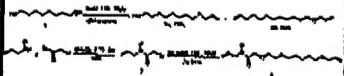


MODEL STUDY

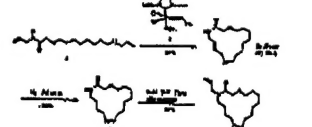
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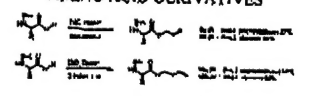
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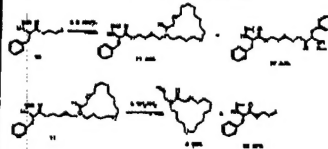


AMINO ACID DERIVATIVES



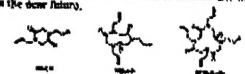
(1) Grubbs, H. C. *J. Am. Chem. Soc.* 1995, 117, 2071.
 (2) Grubbs, H. C.; Ziegler, R. M. *J. Am. Chem. Soc.* 1996, 118, 5171.
 (3) Grubbs, H. C. *Chem. Rev.* 1998, 98, 1071.

CROSS-METATHESIS



CURRENT EFFORTS

The Model Study has demonstrated the reversibility of the cross-metathesis reaction of an allyl ester of amino acid with N-allyl lactam, a key toward creating a dynamic library. Based on these studies, we are synthesizing N-allyl lactams with various number of "beams" (three, trimer, and tetramer). In the current studies, a small library of cyclic peptidomimetics was generated. Various templates are now being examined to shift the equilibrium where only one major cross-metathesis of the library is formed. Results of these studies will be released in the near future.



ACKNOWLEDGEMENTS

Grubbs Group Members:
 Joel Hwang, Sophie Klein, Ryan Martin, and Katelyn Mendel

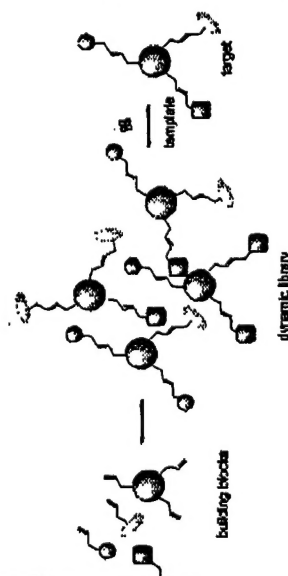


Ring-Closing Metathesis of Macrocyclic Compounds and Cross-Metathesis of Allyl Ester of Amino Acids Leading to Peptidomimetic

TAMMY K.C. LOW and ERIC J. ENHOLM

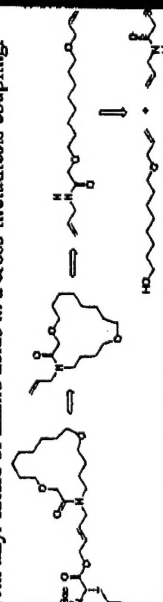
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MODEL STUDY

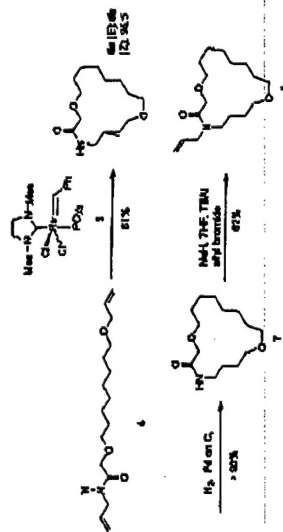
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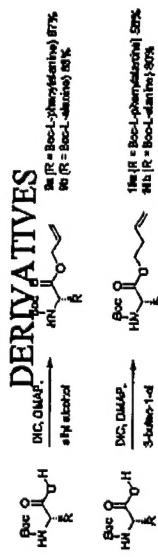
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LACTAM

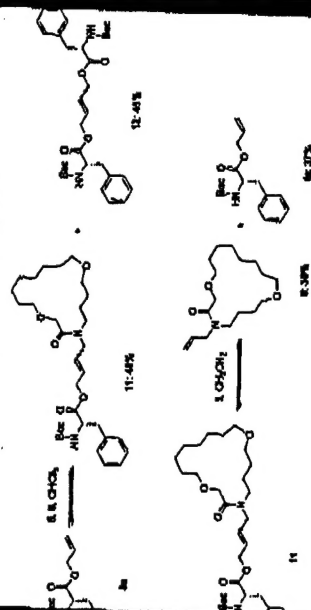


AMINO ACID DERIVATIVES



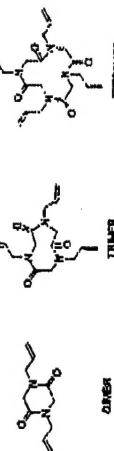
¹Blackwell H. E. et al. *J. A. Chem. Soc.* 2000, 122, 58-71
²Reichwein, J. F.; Lickamp, B. M. *J. Eur. J. Org. Chem.* 2000, 12, 2335-2344
³Enholm, E. J. et al. *Journal of Organic Chemistry* 2004, 69, 1035-1044

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ACKNOWLEDGEMENTS

Enholm Group Members:
 Jed Hastings, Sophie Klein, Ryan Martin, and Kalyan (Mandal)